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Review

The future of sudden cardiac death research

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ABSTRACT

Sudden unexplained death (SUD) in the young is a rare but tragic event. As genetic cardiac causes underlie the majority of SUD cases, surviving family members with the same genetic substrate as their deceased relative may be at increased risk. Presently, the diagnostic strategy to young SUD victims and their families is yet not standardized, the underlying aetiology in an important fraction of cases is still unravelled, and risk prediction in the genetically affected relatives is difficult due the variable expressivity of disease-causing mutations. In this review, we describe an ideal approach to SUD that is currently feasible but unfortunately not routinely followed in the clinical practice. We also discuss recent advancements in genetic technology and novel insights in the pathomechanism of genetic diseases that provide new opportunities for the future of sudden cardiac death research and management.

1. Introduction

Although sudden unexplained death (SUD) in the young is statistically uncommon, affecting <5 per 100.000 persons per year [1], the sudden and unanticipated loss of an apparently healthy child or young adult remains a great tragedy with disastrous implications for the surviving family and the society. Over the last two decades, our understanding of the cardiac causes of SUD (i.e., sudden cardiac death [SCD]) has increased importantly by the discovery of a genetic basis for a number of various cardiac diseases and the identification of the same genetic substrates in a significant portion of SCD cases, including at least one-third of cases with structural cardiac changes at autopsy and up to one-third of cases where no cause of death is identified at post-mortem, so-called sudden arrhythmia death syndrome (SADS) [2]. Structural genetic diseases underlying SCD include hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), dilated cardiomyopathy (DCM), and left ventricular non-compaction cardiomyopathy (LVNCC). Non-structural arrhythmogenic genetic diseases underlying SADS are ion channel diseases such as long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and idiopathic ventricular fibrillation (IVF). All these diseases are associated with an increased risk of life-threatening ventricular arrhythmia and, thereby, SCD, In addition, they are, in the majority of cases, inherited in an autosomal-dominant manner, meaning that first-degree relatives have 50% chance of carrying the same genetic substrate (i.e., disease-causing mutation). Hence, ascertainment of a genetic basis for SCD has enabled not only better identification of the cause of SCD, providing an explanation for the death of numerous children or young adults, but also timely diagnosis of the surviving family members who carry the same mutation and its associated risk as their deceased relative [3]. Unfortunately, despite these major advances, the cause of SCD in at least two-third of cases is still unknown [2]. Moreover, the use of genetic testing to identify family members at the highest risk for preventive measures and prophylactic treatment is hampered by the fact that for a given family member carrying the familial mutation does not automatically mean that he or she will develop disease [4–5]. It remains largely elusive why relatives carrying the same (identical) mutation display large variability in disease severity ranging from SCD at young age all the way to lifelong asymptomatic state. As a result, it remains difficult to predict which family member with the same mutation as the deceased relative will also suffer a SCD, and this poses great uncertainty to family members and treating physicians.

In this review, we will first illustrate an ideal approach to young SUD victims that is theoretically feasible with the currently available knowledge and expertise, but unfortunately not always followed in the routine clinical practice (see Fig. 1). Awareness of its importance and

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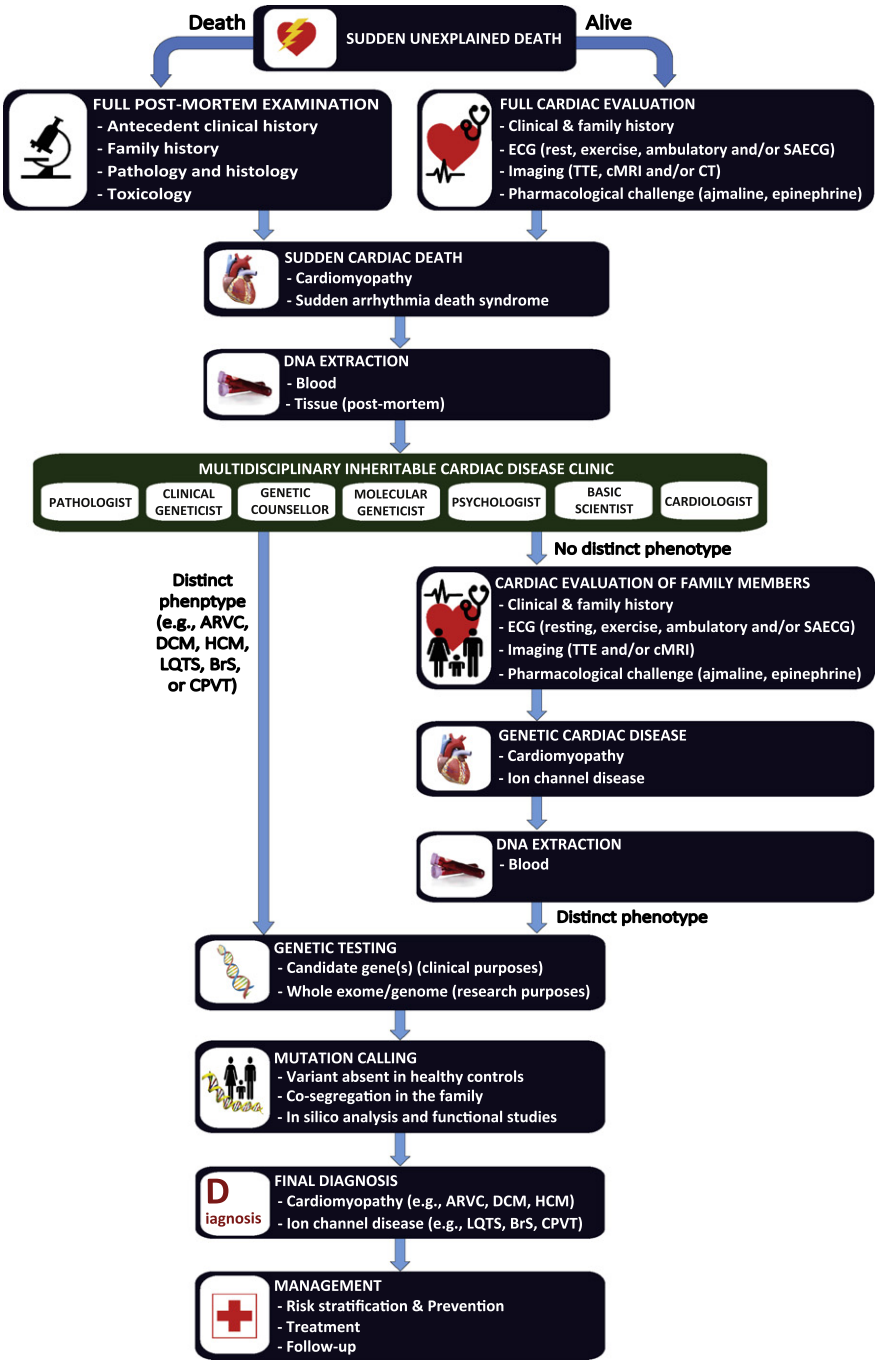

Fig. 1. An ideal approach to victims of sudden of unexplained death (SUD). Algorithm to describe an ideal (currently feasible) diagnostic strategy for the identification of a cardiac genetic cause in victims of SUD and their families. ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; cMRI: cardiac magnetic resonance imaging; CT; computer tomography scanning; CPVT, catecholaminergic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; SAECG: single-averaged ECG; TTE: transthoracic echocardiogram.

conjoint commitment to pursue the best possible approach to SUD should be our initial goal in the near future. Next, we will discuss recent promising advances in genetic technology and insights in pathomechanism of genetic cardiac diseases that may provide new opportunities for better identification of the cause of SCD and better risk stratification of SCD in the surviving family members. Other major aspects of SUD and SCD in the young are discussed elsewhere in this issue of *Progress in Pediatric Cardiology* and will not be repeated here, including the causes of SUD in the young, the role of post-mortem and in particular the role of molecular autopsy, investigation and psychological assistance of family members of SCD victims, and prevention of SCD in the population.

2. The present: an ideal approach to SCD

2.1. An ideal approach to SUD cases

SUD of the young occurs often outside of the hospital (usually at home) and is then referred to as out-of-hospital cardiac arrest (OHCA) [1]. After OHCA, different scenarios may follow: the victim receives cardiopulmonary resuscitation (CPR), reaches the hospital and survives (i.e., aborted SUD), the victim dies after reaching the hospital, or the victim dies outside of the hospital. Currently, for neither of these scenarios is the work-up standardized yet by national or international guidelines. As a result, post-mortem examination (autopsy) is not mandatory in